

SYSTEMATIC REVIEW

Congenital anomalies and maternal age: A systematic review and meta-analysis of observational studies

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Abstract

Introduction: Several studies have reported on the maternal age-associated risks of congenital anomalies. However, there is a paucity of studies with comprehensive review of anomalies. We aimed to quantify the risk of birth defects in children born to middle-aged mothers compared with that in children born to young or older mothers.

Material and methods: We classified maternal ages into three groups: young (<20 years old), middle (20–34 years old) and older age (≥35 years old). Observational studies that met our age criteria were eligible for inclusion. The articles searched using the Embase and MEDLINE databases were those published from 1989 to January 21, 2021. The Newcastle–Ottawa scale was used to assess the risk of bias. If heterogeneity exceeded 50%, the random effect method was used; otherwise, the fixed-effect method was used. Prospero registration number: CRD42021235229.

Results: We included 15 cohort, 14 case-control and 36 cross-sectional studies. The pooled unadjusted odds ratio (95% CI) of any congenital anomaly was 1.64 (1.40–1.92) and 1.05 (0.95–1.15) in the older and young age groups, respectively (very low quality of evidence). The pooled unadjusted odds ratio of chromosomal anomaly was 5.64 (5.13–6.20) and 0.69 (0.54–0.88) in the older and young age groups, respectively. The pooled unadjusted odds ratio of non-chromosomal anomaly was 1.09 (1.01–1.17) and 1.10 (1.01–1.21) in the older and young age groups, respectively (very low quality of evidence). The incidence of abdominal wall defects was increased in children of women in the young maternal age group.

Conclusions: We identified that very low quality evidence suggests that women in the older maternal age group had increased odds of having children with congenital anomalies compared with those in the 20–34 year age group. There was no increase in odds of children with congenital anomalies in women of <20 year age group except for abdominal defects compared with those in the 20–34 year age group. The results stem from very low quality evidence with no adjustment of confounders.

Damin Ahn, Jieon Kim, Junyeong Kang and Yun Hak Kim contributed equally to this work as first authors.

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KEYWORDS

adolescent pregnancy, chromosomal anomalies, congenital abnormalities, late childbearing, non-chromosomal anomalies

1 | INTRODUCTION

Congenital anomalies refer to structural or functional birth defects.¹ As the average age of pregnancy in current times is older than that in the past, birth defects are emerging as an important topic in clinical care and public health.¹ In some cases, congenital anomalies occur due to known causes such as single gene mutation, chromosomal abnormalities and environmental factors; however, there are many anomalies with unknown causes.² It has been reported that approximately one in 33 newborns has congenital anomaly.³ The prevalence of major birth defects does not have significant racial differences. However, there may be differences in the prevalence of some birth defects (eg neural tube defects depending on folic acid supplementation) owing to differences in cultural and social environments.⁴ The socioeconomic burden of birth defects is also increasing, with an estimated annual hospital expenditure of \$2.6 billion in the USA.⁵

In the USA, from 2010 to 2019, the mean age of motherhood rose from 27.7 to 29.1 years as the proportion of mothers aged ≥ 35 years increased.⁶ Similarly, in Europe, the mean age of motherhood showed an upward trend from 28.8 years in 2013 to 29.4 years in 2019.⁷ The proportion of childbearing women aged ≥ 35 years increased from 15.4% in 2009 to 33.4% in 2019 in Korea (2019).⁸ Down syndrome, one of the most common chromosomal abnormalities, occurs in one of 400 and one of 12 pregnancies in 35- and 45-year-old women, respectively.⁹

Lean et al. recently published a study on the relation between maternal age and adverse pregnancy outcomes.¹⁰ However, to our knowledge, systematic reviews and meta-analyses of the association between maternal age and congenital anomalies have not been published. This study aimed to evaluate quantitatively the risk of having children with congenital anomalies in young or older mothers compared with that risk in the reference group (mothers aged 20–34 years).

2 | MATERIAL AND METHODS

2.1 | Eligibility criteria

We analyzed studies which reported both major (eg neural tube defect) and minor (eg hydrocele) congenital anomalies. Maternal age was classified into three groups: young mothers (<20 years old), reference group (20–34 years old) and older mothers (≥ 35 years old). Cohort, case-control and cross-sectional studies were eligible for inclusion.

Key message

The odds increased in the older maternal group, but not in the young maternal group except for an abdominal wall defect. Because our results are very low quality evidence with no adjustment of confounders based on observational studies, caution is required in interpreting the results.

2.2 | Information sources and search strategy

This systematic review was conducted in accordance with PRISMA guidelines.¹¹ The protocol of this study was registered at PROSPERO (registration number: CRD42021235229). We searched for articles published from 1989 to January 21, 2021, using Embase and MEDLINE databases. The search terms were as follows: (maternal age, reproductive age, late pregnancy, older mother, maternal risk, maternal factor, maternal variable) AND (congenital anomal* OR deformit* OR birth defect\$ OR fetal malformation\$ OR fetal anomal*) AND (risk OR ratio OR prevalence OR incidence OR morbidity OR odds OR hazard OR outcome). The search was limited to titles and abstracts. Only articles published in English were included but we did not restrict the publication year. We included published articles or articles in press among the searched materials.

2.3 | Selection process

The literature search was conducted independently by three authors (DA, JK, JK), and the title and abstract for each study were checked thoroughly. The full-text articles were reviewed by the same authors for inclusion. Any disagreements were resolved via discussion.

2.4 | Data collection process and data items

We extracted the following data during the screening phase: title, abstract, journal, author name, publication year and publication type. Through a full-text assessment, additional data on the authors, study design, age, effect measures, number of samples, period, World Health Organization region, race/ethnicity and data source were extracted. We included studies that presented the number of samples or effect measures (eg risk ratio, odds ratio and prevalence ratio) according to our age criteria. Studies without available data were excluded when they did not match the age criteria set in this study. All studies were included even if the database was duplicated, but the types of anomalies reported were different.

2.5 | Assessment of risk of bias

The Newcastle–Ottawa scale was used to assess qualitatively the risk of bias for the included cohort and case–control studies.¹² For cross-sectional studies, the adapted version of the Newcastle–Ottawa scale presented by Herzog et al. was used.¹³ The authors (DA, JK, JK) independently assessed the risk of bias of the included studies and verified the quality of the evidence. Any discrepancy in the assessment was resolved via discussion.

2.6 | Effect measures

It was assumed that the relative risk and odds ratio could be numerically integrated because congenital anomalies are rare diseases in the target population.¹⁴ Schmidt and Kohlmann suggested a “rare disease assumption” that odds ratio may provide an acceptable approximation of relative risk.¹⁴ This could be applied when the prevalence or incidence did not exceed 10% in the target population.¹⁴ Since the overall incidence of congenital anomalies is reported to be approximately 3%, we assumed that the odds ratio could be numerically integrated into the relative risk.³ We integrated several effect measures, such as odds ratio, relative risk, prevalence ratio and risk ratio, into odds ratios. The number of samples was used first for the odds ratio calculation, followed by the unadjusted value and 95% confidence interval (CI).

2.7 | Synthesis methods

We performed meta-analyses to calculate the pooled odds and the corresponding 95% CI stratified according to maternal age. The classification of I^2 statistics as presented by Higgins et al. was used to evaluate the heterogeneity of the effect measures.¹⁵ The heterogeneity was considered low, moderate and high for I^2 values of 25%, 50% and 75%, respectively. We considered an I^2 value >50% to indicate substantial heterogeneity. If heterogeneity exceeded 50%, the random effects method was used; otherwise, the fixed effects method was used. If an integrated value was required within the study, the calculations were performed using the Higgins method.¹⁵ We considered the results to be statistically significant when the P -value was <0.05 or when the CI did not include 1. REVIEW MANAGER 5.4 software was used to synthesize results.

We conducted sensitivity analyses restricted to studies with recent publication (2000 or later); overall low risk of bias (rated as “good” based on Newcastle–Ottawa scale); and individual study design (cohort, case–control and cross-sectional design).

Subgroup analyses were conducted for mothers aged 35–39 years, mothers aged ≥40 years, chromosomal/non-chromosomal anomalies, and organ system defects.

Organ system defects were divided into eight categories: central nervous system defects, oral cleft/lip defects, heart defects, digestive system defects, abdominal wall defects, diaphragmatic hernias, limb and extremity defects, and urogenital defects.

2.8 | Publication bias

Funnel plots were drawn to evaluate the risk of publication bias using the REVIEW MANAGER 5.4 software. Egger's regression test was performed using STATA 13 software to evaluate statistically the publication bias.

2.9 | Certainty assessment

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to evaluate the strength of the clinical practice recommendations. This approach uses a structure that rates the confidence in risk estimates as high, moderate, low, or very low, based on eight considerations: study limitation, directness, consistency, precision, reporting bias, dose–response association, plausible confounders that would decrease the observed effect, and strength of association (magnitude of effect).¹⁶ For observational studies the assessment starts at “low” level and further upgrading or downgrading is carried out based on responses from domain criteria described above.

3 | RESULTS

3.1 | Study selection and characteristics

A total of 2504 records were initially found based on the search terms. We excluded non-humans, non-article types and conference papers. Overall, 1155 records were screened based on their titles and abstracts. Further, 962 papers not related to our study topic were excluded. A full-text review of 193 papers was conducted, and 87 papers were selected. We excluded 106 papers according to the following criteria: duplicated papers, review articles, non-English articles, no full-text available, no quantitative data, and no control group. Twenty-three papers were excluded owing to mismatched age criteria. Finally, 65 papers were included (Figure 1). These included 15 cohort, 14 case–control and 36 cross-sectional studies. The characteristics of the included studies are presented in Table 1.

3.2 | Synthesis of results

3.2.1 | Overall congenital anomaly

Sixty-two and 52 studies were included in the analyses of older and young mothers, respectively. The pooled unadjusted odds ratio of congenital anomaly (95% CI) was 1.64 (1.40–1.92) ($I^2 = 99\%$) and 1.05 (0.96–1.15) ($I^2 = 88\%$) in the pregnancies of older and young mothers, respectively (Figure 2A,B). A subgroup analysis of the groups including mothers aged 35–39 years and those aged ≥40 years was performed based on 17 studies. The pooled unadjusted odds ratio of congenital anomaly was 1.72 (1.39–2.11) ($I^2 = 98\%$) and 3.24 (2.04–5.15) ($I^2 = 99\%$) in the groups with mothers aged 35–39 years and those aged ≥40 years, respectively.

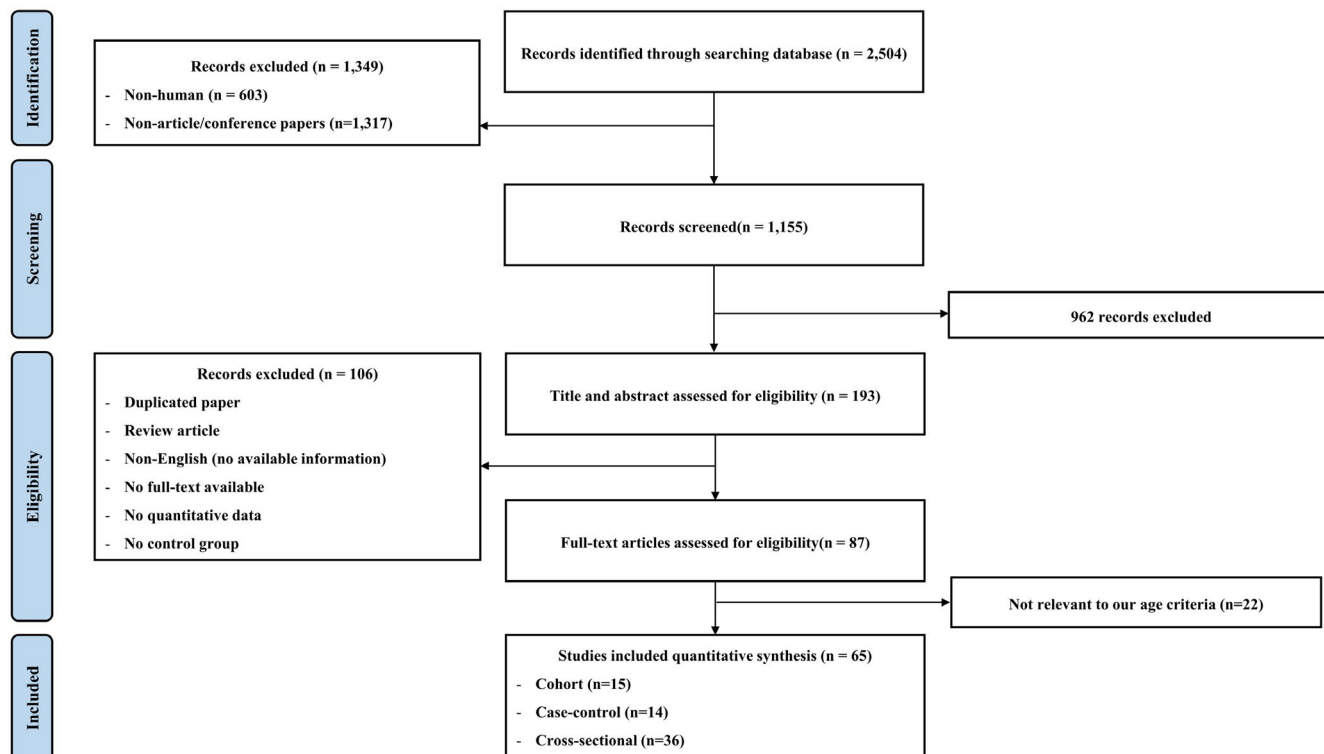


FIGURE 1 PRISMA flowchart

3.2.2 | Chromosomal anomaly

In all, 14 studies and 11 studies were included in the analyses of older and young mothers, respectively. The pooled unadjusted odds ratio of chromosomal anomaly was 5.64 (5.13–6.20) ($I^2 = 87\%$) and 0.69 (0.54–0.88) ($I^2 = 78\%$) in pregnancies of older and young mothers, respectively. In older mothers, the unadjusted odds ratio of having a child with trisomy 13, 18 and 21 was 2.98 (1.30–6.78) ($I^2 = 98\%$), 5.06 (2.40–10.65) ($I^2 = 99\%$) and 6.70 (4.78–9.40) ($I^2 = 98\%$), respectively, whereas those for young mothers, were 0.88 (0.72–1.09) ($I^2 = 37\%$), 0.93 (0.79–1.09) ($I^2 = 0\%$) and 1.01 (0.94–1.08) ($I^2 = 0\%$), respectively.

3.2.3 | Non-chromosomal anomaly

In all, 15 and 14 studies were included in the analyses of older and young mothers, respectively. The pooled unadjusted odds ratio of having a child with a non-chromosomal anomaly was 1.09 (1.01–1.17) ($I^2 = 62\%$) and 1.10 (1.01–1.21) ($I^2 = 57\%$) in older and young mothers, respectively.

3.2.4 | Differences in organ system defects

A subgroup analysis was performed for eight organ system defects: central nervous system defects, oral cleft/lip defects, heart defects, digestive system defects, abdominal wall defects, diaphragmatic hernias, limb and extremity defects, and urogenital defects.

The overall results are presented in Table 2. The heterogeneity was considerable except for that in the results of oral cleft/lip defects and diaphragmatic hernias. In children of older mothers, the incidence of central nervous system defects, oral cleft/lip defects, heart defects and urogenital defects was significantly increased. In young mothers, the incidence of having children with oral cleft/lip defects and abdominal wall defects was significantly increased.

3.3 | Sensitivity analysis

The sensitivity analysis was performed based on the parameters: recent publication, overall low risk of bias, and individual study design. The magnitude of the pooled effect remained relatively similar in sensitivity analyses (Table 3).

3.4 | Risk of bias within studies

We assessed the quality of included studies based on the Newcastle–Ottawa scale. The quality of most studies was rated “good.” Detailed assessments are presented in Tables S1–S3.

3.5 | Publication bias across studies

Funnel plots were drawn for results of overall congenital anomalies (Figures S1 and S2). Egger's regression test confirmed that no

TABLE 1 Characteristics of studies

Source	Study design	Age	Effect measures	Number of samples	Period	WHO region	Race/ethnicity	data source
Jiang ¹⁷	Cohort	<20, 20–24 (Ref), 25–29, 30–34, ≥35	RR	Screening group (n = 63 175) Control group (n = 649 862)	2013–2017	China		74 hospitals and Maternal and Children Health Care Centers of the Dongguan city
Yang ¹⁸	Cohort	<20, 20–34, ≥35	Number	Congenital heart defect (n = 987) Non-congenital heart defect (n = 60 897)	2015–2019	China		population-based birth cohort in Foshan, China
Bruckner ¹⁹	Cohort	15–24, 25–29, 30–34, ≥35	Number	Down syndrome (n = 2748) Non-Down syndrome (n = 849 094)	1983–2015	France		Paris Registry of Congenital Malformations
Bishop ²⁰	Cohort	<20, 20–34 (Ref), >34	RR (risk ratio)	n = 12 450	2007–2011	UK	White British, Pakistani, Other	Born in Bradford (BiB) prospective birth cohort.
Louis ²¹	Cohort	<20, 20–24, 25–29, 30–34, ≥35	Number	n = 13 108 466	1999–2007	US	Non-Hispanic white, Non-Hispanic black, Hispanic, and Asian/Pacific Islander.	11 population-based birth defects surveillance programs
Bhat ²²	Cohort	20–24, 25–29, 30–34, ≥35	Number	n = 20 432	2012–2014	North India		a tertiary care center,
Berg ²³	Cohort	<20, 20–24, 25–29 (Ref), 30–34, 35–39, ≥40	RR (relative risk)	Cases (n = 3353) Total (n = 2 552 612)	1967–2010	Norway		The nationwide Medical Birth Registry of Norway (MBRN)
Marshall ²⁴	Cohort	<20, 20–24, 25–29 (Ref), 30–34, ≥35	Prevalence rate	Cases (n = 2308) Total (n = 12 006 912)	1995–2005	US	Non-Hispanic white, Non-Hispanic black, Hispanic, Other	12 state population-based birth defects registries
Mburia-Mwalili ²⁵	Cohort	<20, 20–24, 25–29 (Ref), 30–34, ≥35	OR (odds ratio)	Cases (n = 4641) Total (n = 124 341)	2006–2011	US	Non-Hispanic white, Non-Hispanic black, Hispanic, and other non-Hispanic	Nevada Birth Outcomes Monitoring System (NBOMS)
Vaughan ²⁶	Cohort	≤17, 18–19, 20–34 (Ref), 35–39, ≥40	OR (odds ratio)	n = 36 916	2000–2011	Ireland		Urban maternity hospital in Ireland.
Weng ²⁷	Cohort	≤14, ≥44, 27 (Ref)	RR (relative risk)	n = 2 123 751	2001–2010	Taiwan		The Birth Notification System (BNS)
Salemi ²⁸	Cohort	<20, 20–24, 25–29 (Ref), 30–34, ≥35	PR	Cases (n = 395) Total (n = 1 179 418)	1998–2003	US	Non-Hispanic white, Non-Hispanic black, Hispanic, Other	The Florida Birth Defects Registry
Glass ²⁹	Cohort	<20, 20–24, 25–29 (Ref), 30–34, 35–39, or ≥40	RR	Cases (n = 630) Total (n = 3 440 576)	1983–2003	U.S.	Non-Hispanic white, US born Hispanic white, Foreign-born Hispanic white, black, Asian	The California Birth Defect Monitoring Program (CBDMP)

TABLE 1 (Continued)

Source	Study design	Age	Effect measures	Number of samples	Period	WHO region	Race/ethnicity	data source
Tuohy ³⁰	Cohort	<20, 20–24, 25–29, 30–34, ≥35	Number	Cases (n = 170) Total (n = 3933)	1990–1991	New Zealand	European, Maori, Pacific Islander, other	The Plunket National Child Health Study
Mishra ³¹	Cohort	<24, 24–34, >34	Number	Cases (n = 60) Total (n = 4038)	1983–1987	India		Swaroop Rani Nehru Hospital
Abebe ³²	Case-control	≤20, 21–25, 26–35, ≥36	Number	Cases (n = 251) Control (n = 887)	2016–2018	Southwestern Ethiopia		6 hospitals in southwestern Ethiopia
Syvänen ³³	Case-control	<25, 25–34 (Ref), ≥35	OR (odds ratio)	Cases (n = 323) Controls (n = 1615)	1996–2008	Finland		Finnish Register of Congenital Malformations
Syvänen ³⁴	Case-control	<25, 25–34 (Ref), >35	OR (odds ratio)	Cases (n = 87) Control (n = 435)	1996–2008	Finland		The National Register of Congenital Malformations, the Medical Birth Register, and the Register on Induced Abortions
Kurdi ³⁵	Nested case-control	<20, 20–30 (Ref), 31–40, >40	OR (odds ratio)	Congenital anomalies (n = 1179) Controls (n = 1262)	2010–2013	Saudi Arabia		tertiary care center, Riyadh, Saudi Arabia
Parker ³⁶	Nested case-control	<20, 20–25, ≥25	Number	Cases (n = 292) Controls (n = 826)	1987–2012	Finland		Finnish Maternity Cohort
Dawson ³⁷	Case-control	<25, 25–29 (Ref), 30–34, >35	OR (odds ratio)	Cases (n = 117) Controls (n = 228)	1997–2007	US	Non-Hispanic white, Non-Hispanic black, Hispanic, Other	The National Birth Defects Prevention Study (NBDPS)
Pawluk ³⁸	Case-control	≤19, 20–34, ≥35	OR (odds ratio)	Cases (n = 3786) Controls (n = 13344)	1992–2001	Argentina		39 hospitals in Argentina
Winston ³⁹	Case-control	<20 (Ref), 20–24, 25–29, 30–34, ≥35	OR (odds ratio)	Cases (n = 995) Controls (n = 16013)	2003–2005	US	Non-Hispanic white, Non-Hispanic black, Hispanic, Other race	The North Carolina Birth Defects Monitoring Program (NCBDMP)
Luo ⁴⁰	Nested case-control	<25, 25–29 (Ref), 30–34, ≥35	OR (odds ratio)	Congenital heart defects (n = 693) polydactyly (n = 352), cleft lip with or without palate (n = 159) equinovarus (n = 119) Controls (n = 11307)	2010–2012	China		The Shenzhen Maternal and Child Health Management System
Gill ⁴¹	Case-control	<20, 20–24, 25–29, 30–34, 35–39, ≥40	Number	Cases (n = 20377) Control (n = 8169)	1997–2007	US	Non-Hispanic white, Non-Hispanic black, Hispanic, Other	The National Birth Defects Prevention Study(NBDPS)
Pate ⁴²	Case-control	<18, 18–24, 25–34 (Ref), ≥35	OR (odds ratio)	Cases (n = 187) Control (n = 6703)	1997–2005	US	Non-Hispanic white, Non-Hispanic black, Hispanic, other	The National Birth Defects Prevention Study(NBDPS)

(Continues)

TABLE 1 (Continued)

Source	Study design	Age	Effect measures	Number of samples	Period	WHO region	Race/ethnicity	data source
Parker ⁴³	Case-control	<23, 23–34 (Ref), ≥35	OR (odds ratio)	Cases (n = 6139) Controls (n = 61390)	2001–2005	US	white black/African American Hispanic Asian American Indian	The National Birth Defects Prevention Network (NBDPN),
Mylvaganam ⁴⁴	Case-control	<20, 20–24, 25–29 (Ref), 30–34, ≥35	OR (odds ratio)	Cases (n = 450) Controls (n = 777)	1980–1994	Australia	Caucasian, Aboriginal, Other	The West Australian Birth Defects Registry (BDR)
Farley ⁴⁵	Case-control	<19, 20–34 (Ref), ≥35	OR (odds ratio)	Cases (n = 224) Controls (n = 930)	1989–1998	US	white, black, Indian, Asian	The Colorado Responds to Children with Special Needs (CRCSN) neural tube defect (NTD) registry
Xie ⁴⁶	Cross-sectional	<20 (Ref), 20–25, 25–30, 30–35, ≥35	Prevalence, OR (odds ratio)	Chromosomal abnormalities (n = 3181) Total (n = 2 883890)	2016–2019	China		1083 hospitals in Hunan Province
Yi ⁴⁷	Cross-sectional	<20, 20–24, 25–29 (Ref), 30–34, ≥35	Prevalence Ratio	n = 13 284 142	2007–2014	China		The Chinese Birth Defects Monitoring Network (CBDMN)
Xie ⁴⁸	Cross-sectional	<20, 20–24, 25–29, 30–34 (Ref), ≥35	OR (odds ratio), Prevalence	n = 673060	2012–2016	China		52 registered hospitals in Hunan
Jaruratanasirikul ⁴⁹	Cross-sectional	<25, 25–30, 30–34, ≥35	Number	n = 186 393	2009–2013	Thailand		1 university hospital, 3 medical education center hospitals, 1 provincial hospital, 34 community hospitals, 421 health-promoting hospitals, and 7 private hospitals
Cragan ⁵⁰	Cross-sectional	<20, 20–24, 25–29, 30–34, 35–39, ≥40	Number	Cases (n = 9678) Liver births (n = 11 110 665)	2009–2013	US	Non-Hispanic white, Non-Hispanic black, Hispanic, Non-Hispanic Asian or Pacific Islander, Non-Hispanic American Indian or Alaska Native	30 birth defects surveillance programs
Best ⁵¹	Cross-sectional	<20, 20–24, 25–29 (Ref), 30–34, ≥35	RR (relative risk)	Cases (n = 4024)	1998–2013	North of England		The Northern Congenital Abnormality Survey (NorCAS)
Jaruratanasirikul ⁵²	Cross-sectional	<20, 20–25, 25–30, 30–35, ≥35	Number	n = 186 393	2009–2013	Thailand		1 university hospital, 3 medical education center hospitals, 1 provincial hospital, 34 community hospitals, 421 health-promoting hospitals, and 7 private hospitals
Jaruratanasirikul ⁵³	Cross-sectional	<20, 20–24 (Ref), 25–29, 30–34, ≥35	Prevalence	n = 186 393	2009–2013	Thailand		467 hospitals in three provinces in southern Thailand

TABLE 1 (Continued)

Source	Study design	Age	Effect measures	Number of samples	Period	WHO region	Race/ethnicity	data source
Bergman ⁵⁴	Cross-sectional	<20, 20–24, 25–29 (Ref), 30–34, 35–39, ≥40	Prevalence, RR (relative risk)	Cases (n = 10 929) Total (n = 5 871 855)	2001–2010	Europe		European Surveillance of Congenital Anomalies (EUROCAT) registries
Deng ⁵⁵	Cross-sectional	<20, 20–24 (Ref), 25–29, 30–34, ≥35	Prevalence	Cases (n = 1933) Total (n = 6 308 594)	1996–2007	China		Chinese Birth Defects Monitoring Network (CBDNMN)
McGivern ⁵⁶	Cross-sectional	<20, 20–24 (Ref), 25–29, 30–34, ≥35	Prevalence, RR (relative risk)	Cases (n = 3373) Total (n = 12 155 491)	1980–2009	Europe		European Surveillance of Congenital Anomalies (EUROCAT) registries
Best ⁵⁷	Cross-sectional	<20, 20–24, 25–29 (Ref), 30–34, ≥35	RR (relative risk)	Cases (n = 1322)	1980–2009	Europe		The European Surveillance of Congenital Anomalies (EUROCAT)
Zhang ⁵⁸	Cross-sectional	<25, 25 ~ 30, 30 ~ 35, >35 (Ref)	Prevalence, RR (relative risk)	n = 976	2005–2008	China	Han, Mongolian, Other	survey of Inner Mongolia Birth Defects Program
Savva ⁵⁹	Cross-sectional	16–49 (All ages specified)	Prevalence	Trisomy 13 (n = 975) Trisomy 18 (n = 2254)	1980–2004	UK, Australia		7 UK regional congenital anomaly registers and 2 Australian registers
Chen ⁶⁰	Cross-sectional	<20, 20–29 (Ref), 30–34, 35–39, ≥40	OR (odds ratio)	Cases (n = 1775) Total (n = 242 140)	2002	Taiwan		the birth registry in Taiwan
Boulet ⁶¹	Cross-sectional	15–19, 20–34 (Ref), 35–44	PR	Cases (n = 281)	1989–2003	US	white Non-white	The Metropolitan Atlanta Congenital Defects Program (MACDP)
Hosani ⁶²	Cross-sectional	16–19, 20–24, 25–29, 30–39, ≥40	Number	Cases (n = 441) Total (n = 68 149)	1999–2001	United Arab Emirates		The National Congenital Anomalies Register
Tan ⁶³	Cross-sectional	<15, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49	Number	Cases (n = 7870) Total (n = 328 096)	1994–2000	Singapore	Chinese, Malay, Indian, Others	The National Birth Defects Registry (NBDR)
Dai ⁶⁴	Cross-sectional	<20, 20–24, 25–29, 30–34, ≥35	Number	Cases (n = 499) Total (n = 2218 616)	1996–2000	China		Chinese Birth Defects Monitoring Network, a hospital-based congenital malformation registry system
Forrester ⁶⁵	Cross-sectional	≤19, 20–24, 25–29 (Ref), 30–34, 35–39, ≥40	RR (rate ratio)	Cases (n = 28) Total (n = 281 866)	1986–2000	US	Caucasian Far East Asian Pacific islander Filipino	The Hawaii Birth Defects Program (HBDP)
Vallino-Napoli ⁶⁶	Cross-sectional	<20, 20–24, 25–29 (Ref), 30–34, 35–39, ≥40	OR (odds ratio)	Cases (n = 1376) n = 1 120 907	1983–2000	Australia		The Victorian Birth Defects Register

(Continues)

TABLE 1 (Continued)

Source	Study design	Age	Effect measures	Number of samples	Period	WHO region	Race/ethnicity	data source
Forrester ⁶⁷	Cross-sectional	≤19, 20–24, 25–29, 30–34, 35–39, ≥40	RR (rate ratio)	Cases (n = 384) Total (n = 258350)	1986–2000	US	white, Far East Asian Pacific islander Filipino	The Hawaii Birth Defects Program (HBDP)
Forrester ⁶⁸	Cross-sectional	≤19, 20–24, 25–29 (Ref), 30–34, 35–39, ≥40	RR (rate ratio)	Cases (n = 352)	1986–2000	US	white, Far East Asian, Pacific Islander, Filipino	The Hawaii Birth Defects Program (HBDP)
Forrester ⁶⁹	Cross-sectional	≤19, 20–24, 25–29 (Ref), 30–34, ≥35	RR (relative risk)	Cases (n = 124) Total (n = 263795)	1986–1999	US	white, Far East Asian Pacific islander Filipino	The Hawaii Birth Defects Program (HBDP)
Hollie ⁷⁰	Cross-sectional	≤15, 16–19, 20–24 (Ref), 25–29, 30–34, 35–39, ≥40	RR (relative risk)	Cases (n = 3757) Total (n = 102728)	1988–1994	US	black, white, Hispanic, Other	Parkland Health and Hospital System
Carothers ⁷¹	Cross-sectional	<15, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, ≥45	Number	Trisomy 21 (n = 470) Trisomy 18 (n = 108) Trisomy 13 (n = 36) Other (n = 32)	1990–1994	UK		The Scottish Trisomy Register (STR)
Byron-Scott ⁷²	Cross-sectional	≤15, 16–19, 20–24, 25–29 (Ref), 30–34, 35–39, ≥40	OR (odds ratio)	Cases (n = 59)	1980–1990	Australia	white, Aboriginal, Asian/Other	The South Australian and Western Australian Birth Defects Registers (SABDR and WABDR)
Himmetoglu ⁷³	Cross-sectional	<20, 21–30, 31–40, >40	Number	Cases (n = 102) Total (n = 9160)	1988–1995	Turkey		Gazi University Faculty of Medicine,
Rasmussen ⁷⁴	Cross-sectional	<20, 20–24, 25–29 (Ref), 30–34, ≥35	RR (risk ratio)	Cases (n = 63) Total (n = 734000)	1968–1992	U.S.	white, Other	The Metropolitan Atlanta Congenital Defects Program (MACDP)
Yoon ⁷⁵	Cross-sectional	<25, 25–34, ≥35 (Ref)	RR (relative risk)	Cases (n = 57)	1968–1993	U.S.	white, Non-white	The Metropolitan Atlanta Congenital Defects Program (MACDP)
Druschel ⁷⁶	Cross-sectional	<20, 20–24, 25–34 (Ref), ≥35	RR (rate ratio)	Cases (n = 60)	1983–1989	US	white, black	The New York State's Congenital Malformations Registry
Lopez ⁷⁷	Cross-sectional	<20, 20–29, 30–34, 35–39, 40+	Number	Cases (n = 173) Total (n = 141784)	1980–1990	UK		The Glasgow Register of Congenital Anomalies
Stoll ⁷⁸	Cross-sectional	<20, 20–24, 25–29, 30–34, 35–39, >40	Number	Cases (n = 217) Total (n = 173805)	1980–1992	Germany		The Strasbourg registry
Chaturvedi ⁷⁹	Cross-sectional	≤24, 25–34, ≥35	Number	Cases (n = 82) Total (n = 3000)	1985–1986	India		Mahatma Gandhi Institute of Medical Sciences, Sewagram, Wardha, and Civil Hospital, Wardha
Martin ⁸⁰	Cross-sectional	<20, 20–24, 25–29, 30–34, ≥35	Number	Cases (n = 170)	1970–1983	US	white, black	The Metropolitan Atlanta Congenital Defects Program
Stone ⁸¹	Cross-sectional	<20, 20–24, 25–29, 30–34, 35+	Number	Cases (n = 153) Total (n = 127108)	1974–1986	UK		The Glasgow Register of Congenital Anomalies

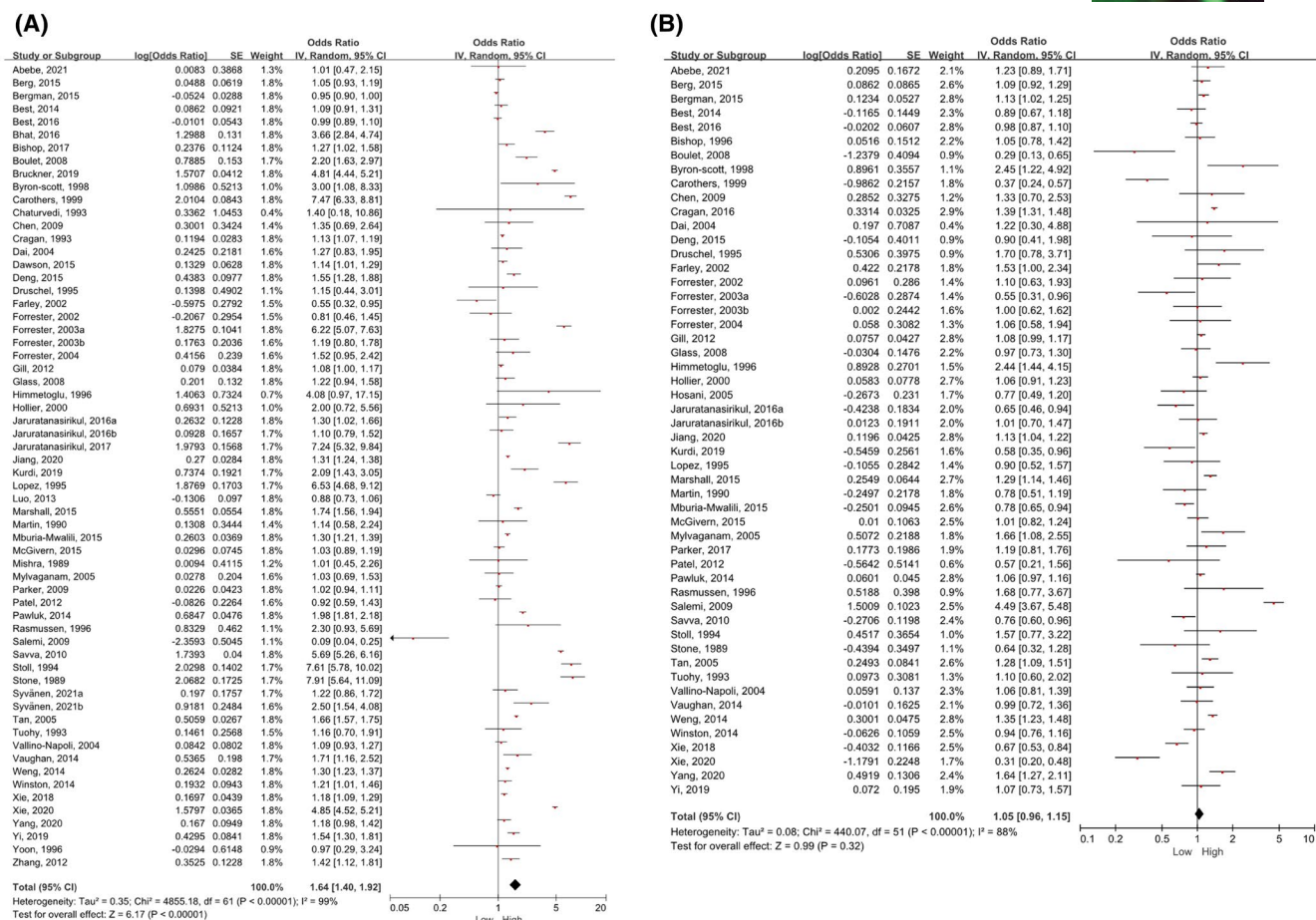


FIGURE 2 Risk of congenital anomalies in (A) older mothers and (B) young mothers compared with reference group

significant publication bias was observed with a $P > 0.05$ in all funnel plots ($P = 0.607$ in older mothers, $P = 0.084$ in young mothers).

3.6 | Certainty assessment

The certainty of evidence was evaluated using the eight domains of the primary outcome. According to the GRADE approach, the quality of the evidence for both cases was rated “very low” (Table 4).

4 | DISCUSSION

In this systematic review and meta-analysis of observational studies, we identified that very low quality evidence suggests that older mothers had an increased unadjusted odds of having a child with congenital anomalies. Edwards syndrome (trisomy 18) and Down syndrome (trisomy 21) showed striking results. There was no increase in unadjusted odds of children with congenital anomalies in women in the <20 year group except for abdominal defects. As a result of the subgroup analysis by organ system defects, very low quality evidence suggests that young mothers had an increased unadjusted odds of having a child with abdominal wall defects.

Biological mechanisms, such as errors in sister chromatid segregation and reduction of chromosome cohesion have been suggested as factors leading to chromosomal abnormalities in oocytes.⁸² It has been suggested that telomere shortening and increased oxygen free radical levels can also reduce the normal chromosomal differentiation of ovarian cells.⁸² Specific congenital anomalies in oocytes, including non-chromosomal defects, have been hypothesized to be associated with increased opportunities for teratogen exposure, accumulation of environmental materials, and increased medical comorbidities, such as gestational diabetes.⁸³ It is thought that a significant positive association with high congenital anomalies found in the fetuses of an older mother might be explained by these factors. Since congenital anomalies, especially chromosomal defects, can cause serious disability by affecting various organs and reducing fetal survival, efforts to prevent defects are necessary for the health of individuals, families and countries.¹

Our study showed that in young mothers, the odds of having children with chromosomal anomalies decreased, whereas that of non-chromosomal anomalies increased; however, the effect was very small. In previous studies, the prevalence of chromosomal defects in US and European populations clearly showed a tendency to increase with maternal age.^{84,85} Several hypotheses have been suggested as the cause of this phenomenon. First, the number of terminations is due to the early detection of congenital anomalies, since adult mothers tend

Organ systems	Number of studies (n)	Heterogeneity (I^2)	Odds ratio (95% CI)
Older mothers (compared with reference group)			
Central nervous system defect	7	92	1.26 (1.03–1.55)
Oral cleft/lip defect	8	45	1.05 (1.01–1.09)
Heart defect	8	54	1.15 (1.06–1.24)
Digestive system defect	6	50	1.07 (0.90–1.28)
Abdominal wall defect	5	99	0.51 (0.19–1.33)
Diaphragmatic hernia	3	85	1.13 (0.84–1.52)
Limb and extremity defect	8	79	1.12 (0.96–1.31)
Urogenital defect	5	97	1.46 (1.13–1.89)
Young mothers (compared with reference group)			
Central nervous system defect	7	86	1.12 (0.92–1.37)
Oral cleft/lip defect	6	0	1.05 (1.01–1.10)
Heart defect	6	83	0.93 (0.79–1.10)
Digestive system defect	5	65	1.17 (0.89–1.55)
Abdominal wall defect	6	98	2.15 (1.26–3.69)
Diaphragmatic hernia	3	0	0.96 (0.87–1.06)
Limb and extremity defect	4	76	1.09 (0.88–1.36)
Urogenital defect	4	88	0.99 (0.81–1.20)

TABLE 2 Subgroup analysis on the difference in risk by organ system defects according to age

Sensitivity analysis	Number of studies (n)	Heterogeneity (I^2)	Odds ratio (95% CI)
Older mothers (compared with reference group)			
Primary analysis	62	99	1.64 (1.40–1.92)
Published in year 2000 or later	49	99	1.48 (1.25–1.75)
Low risk of bias	50	99	1.60 (1.33–1.92)
Cohort	14	99	1.39 (1.06–1.84)
Case-control	13	93	1.20 (1.00–1.44)
Cross-sectional	35	99	2.00 (1.56–2.58)
Young mothers (compared with reference group)			
Primary analysis	52	88	1.05 (0.96–1.15)
Published in year 2000 or later	41	90	1.04 (0.95–1.15)
Low risk of bias	43	90	1.02 (0.91–1.15)
Cohort	11	95	1.28 (1.02–1.61)
Case-control	9	52	1.08 (0.97–1.21)
Cross-sectional	32	84	0.94 (0.83–1.07)

TABLE 3 Sensitivity analysis according to publication year, risk of bias, and study design

to receive adequate prenatal care.^{86–88} According to Chen et al., only 70% of teenage mothers initiated prenatal care in the first trimester of pregnancy.⁸⁹ In contrast, nearly 90% of adult mothers initiated prenatal care in the first trimester.⁸⁹

Secondly, in young mothers, early exposure to risk factors such as tobacco, alcohol and illicit drugs may explain the etiology. In the USA and the UK, the smoking rate in teenage pregnancies is much higher than that in adult pregnancies.^{89,90} Wong et al. conducted a retrospective cohort study through the Canadian perinatal and neonatal database, and reported that the rates of tobacco, alcohol, marijuana, opioids

and cocaine use among teenage mothers were significantly higher than those among adult mothers.⁹¹ Thirdly, nutrient deficiencies, such as folic acid intake problems, may be associated with certain birth defects such as neural tube defects and gastrointestinal tract malformation.^{92,93}

We performed subgroup analyses by organ system defects and obtained noteworthy results. For older mothers, the overall odds of having a child with congenital anomaly with organ system defects tended to increase. In contrast, there was no significant difference in the odds for most congenital anomalies by organ system defects in adolescent pregnancies, except for abdominal

TABLE 4 GRADE approach for the primary outcome

Quality assessment									
Outcome	Required domains			Additional domains				Grade	
	Study limitations	Consistency	Directness of evidence	Precision	Reporting bias	Dose-response association	Plausible confounding that would decrease observed effect		Strength of association (magnitude of effect)
Older mothers	Low ^a	Inconsistent ^b	Direct	Precise	Undetected ^c	Undetected	Present ^d	Weak ^e	⊕○○○ Very low
Young mothers	Low ^a	Inconsistent ^b	Direct	Precise	Undetected ^c	Undetected	Present ^d	Weak ^f	⊕○○○ Very low

Abbreviation: GRADE, Grading of Recommendations, Assessment, Development and Evaluations.

^aAll included studies are observational, and there are studies where risk of bias is rated as "poor."

^bConsiderable heterogeneity ($I^2 > 75\%$).

^cAccording to Egger's regression test.

^dDrug use, obesity, alcohol consumption, smoking, folic acid supplementation, gestational diabetes and preeclampsia.

^eOR = 1.64.

^fOR = 1.05.

wall defects and oral cleft/lip defects. Although there are several papers showing positive associations between oral cleft/lip defects and older age of mothers, the comprehensive associations may be inconclusive.⁹⁴ In addition, little seems to be known about the association between oral cleft/lip defects and young age of mothers. Surprisingly, in the current study, only abdominal wall defects showed an inverse association with maternal age, and the odds was more than double in women of the young maternal age group.

Our study has several limitations. It is difficult to identify clearly a causal relation between congenital anomalies and maternal age because most of the included studies had a cross-sectional design. No adjustment was made for several risk factors which could be considered potential confounders, such as specific drug use, obesity, alcohol consumption, smoking, folic acid supplementation, gestational diabetes and preeclampsia. Different definitions of age criteria may result in selection bias due to the exclusion of studies. The diagnostic methods for congenital anomalies may have differed between studies due to changes in diagnostic criteria and advances in technology. Some of the included studies had identical registries, which may have resulted in selection bias in the study population. We restricted the eligibility of the studies to those published in English only. The search was performed using the Embase and MEDLINE databases. We did not contact the study authors directly to clarify any information.

Despite these limitations, our study had several strengths. Since many studies utilized national registries, the source was reliable and contained many samples. In addition, external validity of the study would be high, since our research included studies from multiple countries and ethnicities worldwide.

5 | CONCLUSION

We identified that very low quality evidence suggests that women in the older maternal age group had increased unadjusted odds of having children with congenital anomalies compared with those in the 20–34 year age group. There was no increase in unadjusted odds of children with congenital anomalies in women of <20 year group except for abdominal defects compared with those in the 20–34 year age group. The results stem from very low quality evidence with no adjustment of confounders.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

KK and YHK conceptualized and designed the study. DA, JKim and JKang collected, selected, and analyzed the data. DA, JKim and J Kang drafted the manuscript. KK and YHK revised the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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